UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,817	08/30/2005	Tosti Jon Mankelow	37945-0070	7832

26633 7590 07/11/2008

HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,817	MANKELOW ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28 and 30-37* is/are pending in the application.

4a) Of the above claim(s) *30-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/29/08, is acknowledged.

2. Claims 25-28 and 30-37 are pending.

3. Claims 30-37 (non-elected species) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 25-28 are under consideration in the instant application as they read on an antagonist of a ligand for an epitope or footprint domain for binding integrins comprising a domain of ICAM-4 and the species of SEQ ID NO: 9.

5. In view of the amendment filed on 4/29/08, only the following rejections are remained.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 25-28 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide consisting of the amino acid sequence of SEQ ID NOs: 9-11 as antagonists of ICAM-4, does not reasonably provide enablement for any "antagonist" of any ligand for the claimed epitope or claimed footprint domain for binding to any integrin in claim 25, in which said antagonist consists of "three, four, five, six , seven, eight, nine or more amino acid residues of said A, C, F, or G strands or said CE loop of ICAM-4" in claim 26, or any antagonist defined by ICAM-4 strand A includes amino acid residues F18, W19 and V20 of ICAM-4 in claim 27, in which said antagonist consists of "any" amino acid sequence as defined in SEQ ID NO: 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 10/29/07.

Applicant's arguments, filed 4/29/08, have been fully considered, but have not been found convincing.

Applicant argues in conjunction with case law that the specification provides various methods of making and characterizing the disclosed and claimed antagonists. The specification at pages 16-23 describes procedures for many embodiments that fall within the claims. Pages 24-27 provide sequence information. All of this disclosure, combined with the level of skill in the art and the expected level of experimentation in the field militate against any rejection based upon enablement.

While page 24-27 discloses strands A, G, F, E, B, C, CE, SEQ ID NOS: 9-12, however, no single antagonist was made to said strands, nor the antagonist were shown to antagonize integrins binding. Besides the antibodies against SEQ ID NOS: 9-11 and 13 (example 3), the specification fails to enable the skilled in the art on how to make and how to use the claimed antagonists of a ligand for the claimed epitopes. It remains the Examiner's position that a person of skill in the art is not enabled to make and use any "antagonist" including antibody, low molecular weight compounds or 1-9 or more amino acid residues from the ICAM-4 strands that binds to the epitope stand to reduce adhesion between ICAM-4 and its ligands. It was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "antagonists". However, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Further, it is recognized in the art that ligands must posses significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design) and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.). The claims encompass alterations in antagonist folding because claims do permit deviation from the amino acid sequences of the consensus regions for a non-native peptide. It would be reasonable to conclude that alterations in peptide folding would lead to a large alteration in binding affinity. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any antagonist such as a simple or complex organic or inorganic molecule, a peptide or antibodies are fraught with uncertainties.

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various antagonist of a ligand for an epitope or footprint domain for binding integrins as claimed comprising FWV motif recited in the instant claims 27-28. The claimed SEQ ID NO: 9 sequence contain nine amino acid residues in length. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to a peptide that exhibits specific binding inhibition to ICAM-4/ligand, and that the relationship between the peptide and its activity was not well understood. There is definite relationship between structure and function. Further, the terms "comprises" in claim 25 and "includes" in claim 27 are open-ended. They would open up the claimed epitopes to include additional unidentified amino acid residues on either or both of the N- or C- termini of given sequence in large amounts. Further, the FWV motif in larger polypeptide molecule would not be for binding to ICAM-4 ligand. The skilled in the art would

conclude that FWV motif buried a larger sequence would not be accessible for binding to ICAM-4 ligand.

While the specification on page 16 lines 18-20 discloses that due to the overlap of the αv integrin and α4β1 binding site with that of the binding site of LFA-1 and Mac-1, we predict that the peptides also inhibit any ICAM-4/LFA-1 or Mac-1 interaction. However, the specification on page 20, lines 17-20 discloses that inhibition of HEL cells (VLA-1) cell binding and HT1080 (αv) cell binding to human and murine ICAM-2Fc with SEQ ID NO: 9 and SEQ ID NO: 10 but not SEQ ID NO: 11. Further on page 22, lines 1-9 discloses that the F and the G strand peptides (SEQ ID NO:10 and 11, respectively) inhibit adhesion whereas the strand A and D (SEQ ID NOs: 9 and 13, respectively) peptides had no effect. This suggest, along with the data already provided of the peptide inhibition of HEL (VLA-4, α4β1) cell-ICAM-4 adhesion, that the area of interaction with α4β1 on ICAM-3 lies in the F and G strands of domain-1. Further, the specification on page 23, lines 12-14, discloses that neutrophil-ICAM-4 adhesion is mediated by β2 integrins (αLβ2 and αMβ2) and that it is likely to involve an interaction with the G and F strands of domain 1 of ICAM-4 as opposed to the A strand. Accordingly, the antagonist defined by ICAM-4 strand A, such as SEQ ID NO: 9 is not the magic bullet for inhibiting all the interaction between ICAM-4 and its ligands. The specific nature of this antagonist effect was confirmed by the specification. Accordingly, it cannot be seen how such peptide would be an antagonist for any ligand for binding any integrins as claimed in claim 25.

Finally, while claim 25 claims the antagonist of a ligand for a specific epitope or footprint domain of ICAM-4. The specification uses either human or murine ICAM-4Fc in the inhibition experiment. The specification fails to show that the cell inhibition via specific integrin only requires strands A and G of domain 1 of ICAM-4, for example, or the claimed strands or footprints as claimed in claim 25.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 25-28 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 10/29/07

Applicant's arguments, filed 4/29/08, have been fully considered, but have not been found convincing.

Applicant traverses the rejection on the ground that the epitope contains the G strand and either the A or F strand, and can be optionally supplemented by W66 on the E strand. This is set forth in the specification at page 2, lines 4-8 and 28-30; page 3, lines 8-9; and original claims 1 and 3,

for example. Furthermore, the specification contains a more than representative number of species sequences that are set forth at pages 9-27. Applicants submit that they have provided both the generalizing text that describes the claimed invention and specific sequences exemplifying aspects of the invention. Applicants concluded that they have described the invention in a manner that is fully compliant with the written description requirement, and therefore applicants respectfully request withdrawal on the rejection

However, the claims are not directed to the sequences but rather to any antagonist of a ligand for an epitope or footprint domain for binding integrin. Besides, antibodies to SEQ ID NOS: 9-11 and 13, no such antagonists were found in the specification. Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (antagonist) to describe the claimed genus, nor does it provide a description of structural features that are common to species (antagonist). The specification provides no structural description of antagonist of a ligand for an epitope or footprint domain for binding integrins other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed antagonists looks like. The specification's disclosure is inadequate to describe the claimed genus of antagonists.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 25-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hermand et al (IDS ref. No. A03).

Hermand et al teach an antagonist (strand A, N-terminal peptide of ICAM-4-D1, i.e., ^{18}**F**^{19}**W**^{20}**V**RMSPEFV^{27} (as claimed in claim 27)) of a ligand (ICAM-4) for an epitope or footprint domain (D1-D2 domain) for binding LFA-1 integrin as claimed in claim 25 (see Fig. 1 in particular), in which epitope comprises the A strand of ICAM-4-D1 beginning at amino acid residues ^{18}**F**^{19}**W**^{20}**V**RMSPEFV^{27} and the G strand of ICAM-4-D1 ^{90}KTRWATSRITA^{100} (see Fig. 1A), wherein the antagonist consists of 5 amino acid residues VGGLE (see strand C in fig. 1) as claimed in claim 26, in which said antagonist defined by ICAM-4 strand A includes amino acid residues F18, W19 and V20 of ICAM-1 as claimed in claim 27.

Furthermore, Hermand et al teach an antagonist (anti-LW mAbs BS46, BS56, and BS87 antibodies of a ligand (ICAM-4) for an epitope or footprint domain (D1-domain) for binding LFA-1 integrin, in which epitope comprises the A strand of ICAM-4-D1 beginning at amino acid residues ^{18}**F**^{19}**W**^{20}**V**RMSPEFV^{27} and the G strand of ICAM-4-D1 ^{90}KTRWATSRITA^{100} (see Fig. 1A and page 26005, 2nd col. in particular). Herman et al further teach that the three mAbs bind the wild-type ICAM-4-Fc protein carrying the two Ig-like domains D1 and D2 as well as to the deletion mutant lacking domain D2 but did not bind the deletion mutant lacking domain D1

(page 26005, 2nd col. in particular). In addition, Herman et al teach that the three antibodies bind did not bind to mutant proteins comprising W19A substitution (see Table 1 and page 26006, 2nd col., in particular). Herman et al concludes that ICAM-4 binds to LFA-1 (CD11a) within Domain 1.

When a claim recites using an old composition or structure (e.g. strand A) and the use is directed to a result or property of that composition or structure (antagonist) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 4/29/08, have been fully considered, but have not been found convincing.

Applicant argues that Hermand et al. discloses in Fig. 1 what amounts to a nearly complete ICAM-4 sequence (from amino acid residues 20-202). Although the sequence includes the FWV motif, the whole molecule that is represented by the sequence would not act as an antagonist as claimed. Indeed, the examiner has recognized that a larger polypeptide comprising the FWV motif may render the motif inaccessible for binding to ICAM-4. See office action at page 5, lines 10-15. Accordingly, a skilled person would recognize that this molecule does not act as an antagonist.

Contrary to Applicant arguments, Hermand et al delineate each strand in Fig. 1 as indicated by the "↔". Furthermore and contrary to Applicant assertion the complete ICAM-4 sequence is 924 amino acids in length. It appears that Applicant is argument under art contradicts Applicant's argument under the enablement rejection regarding the motif. Applicant claims antagonist defined by ICAM-4 stand A "includes" amino acid residues FWF of ICAM-4. The reference teachings meet the claimed elements of the claims. If the specification is enabling, so is the prior art reference and vice versa.

Applicant further submits that there is no evidence in Hermand et al. that the monoclonal antibodies bind the specific epitopes defined, and thus this rejection is unsubstantiated.

It is the Examiner's position that Hermand et al teach an antagonist (anti-LW mAbs BS46, BS56, and BS87 antibodies) of a ligand (ICAM-4) for an epitope or footprint domain (D1-domain) for binding LFA-1 integrin, in which epitope comprises the A strand of ICAM-4-D1 beginning at amino acid residues ^{18}**F**^{19}**W**^{20}**V**RMSPEFV^{27} and the G strand of ICAM-4-D1 ^{90}KTRWATSRITA^{100} (see Fig. 1A and page 26005, 2nd col. in particular). Herman et al further teach that the three mAbs bind the wild-type ICAM-4-Fc protein carrying the two Ig-like domains D1 and D2 as well as to the deletion mutant lacking domain D2 but did not bind the

deletion mutant lacking domain D1 (page 26005, 2nd col. in particular). In addition, Herman et al teach that the three antibodies bind did not bind to mutant proteins comprising W19A substitution (see Table 1 and page 26006, 2nd col., in particular). Herman et al concludes that ICAM-4 binds to LFA-1 (CD11a) within Domain 1. In addition Hermand et al teach the polyclonal antibody against the N-terminal 15 amino acids of ICAM-4/LW (see page 26003, under Reagents and antibodies in particular).

11. Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bailly et al (IDS Ref No. A01) as is evidenced by the provisional Applicant No. 60/423,391 at page 1.

Bailly et al teach the N-terminal peptide sequence antagonist of the LW (ICAM-4) glycoprotein AQSPKGSPLASG(G)SV**PFXVRM(S)**(P) which has an amino acid sequence as defined in claimed SEQ ID NO: 9, wherein X is undetermined amino acid. The peptide has more amino acid residues of A strand as claimed in claim 26, in which said peptide defined by ICAM-4 strand A includes amino acid residues F18, W19 and V20 of ICAM, as claimed in claim 27 (see table 1). X being W is inherent property of the N-terminal peptide sequence of ICAM-4, as is evidenced by provisional Application No. 60/423,391 at page 1, that the amino acid X at position 18 is W in the mature human ICAM-4 sequence. Further Bailly et al teach the peptide WATS(R) (see table 1) which consist of 5 amino acid residues. WATSR is located at amino acid position 93-97 of ICAM-4.

Applicant's arguments, filed 4/29/08, have been fully considered, but have not been found convincing.

Applicant submits that Bailey discloses a (partially not determined) N- terminal sequence in Fig. 1A that includes the FWV motif and which therefore, according to the examiner, anticipates claims 25-28. However, the N-terminal peptide sequence provided in Fig. 1A was derived from N-terminal sequencing of ICAM-4 and does not represent a distinct molecule, but rather a partial amino acid sequence characterization of the entire ICAM-4 molecule. A sequence, in the absence of other teachings, is not a molecule. Bailly was never in possession of a molecule as recited in the claims, and therefore could never disclose nor enable such a molecule.

It is the Examiner's position that the referenced N-terminal peptide sequence would act as antagonist of the ICAM-4 for an epitope or footprint domain for binding integrins. Further, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Also, as restated in the court in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999). "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 8, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644